

Dosimetry Modeling of
Inhaled Toxic Reactive Gases

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DOSIMETRY MODELING OF INHALED TOXIC REACTIVE GASES

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16. ABSTRACT This chapter focuses on the physical, chemical and biological processes and factors involved in the absorption of reactive gases. Emphasis is placed on the importance of these factors in developing dosimetry models, special consideration being given to the role of lung fluids and tissues. Several dosimetry models are discussed and illustrations of predicted results presented to demonstrate the application of the models to the uptake of NO ₂ and O ₃ , and to demonstrate the use of models in determining the effects of physical, chemical and biological parameters on dosimetry predictions. Gaps in our knowledge and understanding of the processes of dosimetry are pointed out and research recommendations made to increase our understanding of the processes and to enhance the development of dosimetry models.		
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INTRODUCTION

Knowledge of dose is the first component of quantitative extrapolation modeling of animal toxicological results to man. In conjunction with dosimetric data, differences in species sensitivity must be addressed to determine if there is equivalency of biological response to comparable delivered doses, and there must be a health effects data base for which extrapolations are desired.

This chapter reviews the absorption of inhaled toxic reactive gases in the respiratory tracts of man and animals. The review emphasizes the concepts and understanding of absorption through the development and use of mathematical dosimetry models. These models facilitate the integration of our knowledge and understanding of physical, chemical and biological processes and factors to predict the uptake and the distribution of absorbed gases in the respiratory tract.

The processes and factors influencing gaseous uptake that are considered in this chapter are mainly those associated with the fluids and tissues of the respiratory tract. Thus, reactive gases (such as CO) which are transferred out of the lung and require a consideration of processes and factors outside the lung are omitted from the review. Transport in airway lumens and airspaces is described in the Chapter by Ultman.

Since dosimetry models represent an integration of our knowledge, they can be used to test concepts and to advance our understanding in several ways: (1) the gathering of information

to develop models identifies areas where information is missing, (2) carrying out sensitivity studies with models can be used to determine parameters and processes needing further research, and (3) comparing predicted results to experimental data can be used to focus our attention on needed theoretical and experimental research. Equally important is the need to obtain data for validating the concepts that form the basis dosimetry models and for refining the models as needed.

As noted earlier, dosimetry models can be used to estimate exposure levels that produce the same dose in different animals of the same or different species for use in comparing toxicological effects, as well as to assist in experimental design. Predicted regional or local doses can be correlated with observed health effects, thereby allowing the prediction of effects in situations for which experiments are not feasible. Ultimately, in order to assess human health effects, models can be used to establish general principles and guidelines for the evaluation and integration of the results of clinical, epidemiologic, and animal studies.

The review begins with a discussion of the role of anatomy and physiology on absorption. Considered are the importance of anatomical models, the physical, chemical and biological nature of the liquid lining, tissue and capillary blood. Physicochemical factors, including solubility, chemical reactions, molecular diffusion, and convective transport are discussed with emphasis on

explanations of the processes and on the type of information required to characterize the processes for use in dosimetry models. The first part of the next section, Dosimetry Modeling, is a survey of dosimetry models. A summary of their major features and assumptions is provided. The second part of the section illustrates the use of models with emphasis on how dosimetry models can be used to understand the importance of specific physical, chemical or biological factors that influence absorption. The last part of the section considers the relationship between dosimetry models and experimental data. Finally, there are summaries of the review and of the research recommendations.

ANATOMICAL, PHYSIOLOGICAL AND CHEMICAL CONSIDERATIONS

Anatomical Models

For a discussion of respiratory tract structure see the chapter by Schlesinger and the chapter by Ultman.

The dimensions of the lumen of the airways and of the airspaces of an animal's respiratory tract are an important characterization of the animal and necessary to know for dosimetry modeling. For example, unequal path lengths to equivalent morphological areas in the same animal or in different animals may result in significantly different doses to the area of concern. Total absorption depends on surface area (e.g., doubling surface area could double the uptake). An incorrect tracheobronchial (TB) volume would result in erroneous estimates of the quantity of gas delivered by convection to the pulmonary region.

Respiratory tract dimensions useful to dosimetry modeling are summarized by anatomical models. One type of model organizes the many branching airways of the lower respiratory tract (LRT airways distal to, and including trachea) into sequential segments (e.g., generations; however, other groupings have been used). Associated with each segment are idealized airways, all airways of a given sequential segment are the same size, each having the average length and diameter of all or some of the actual or real airways associated with the segment. The pulmonary region can be characterized by specifying the volume and surface area of the average alveoli as well as the number of alveoli per airway.

Probably the best known LRT anatomical model is the one developed by Weibel (1963) for man. The branching structure of the airways is assumed dichotomous. There is only one unique path from the trachea to a given terminal unit, an alveolar sac; however, all of the paths (~ 8.4 million) are equivalent requiring that one path only be considered for dosimetry modeling purposes.

More recently, anatomical models have been developed that take into account some of the actual variability in different paths. The models of Yeh and Schum (1980) for human lungs and of Yeh et al. (1979) for rat lungs are examples. In addition to a model for the whole lung(s) of each species, these investigators also reported lobar models. With more detailed anatomical models such as these, dosimetry modelers can investigate the effects of intra-lung differences on predicted uptake and on dose at equivalent but differently located morphological sites.

Most LRT anatomical models are not based on morphometric measurements made at normal breathing lung volumes (e.g., Weibel, 1963; Yeh et al., 1979; Yeh and Schum, 1980). To use such data for dosimetry modeling, the data should be modified to better represent the lung size for the breathing conditions being considered. Procedures for changing reported lung dimensions to those experienced during a breathing cycle are needed.

Upper respiratory tract (URT, airways proximal to trachea) dimensions also have been reported in terms of sequential segments along the path of air flow. Dimensions of the URT's of several animals are given by Schreider and Raabe (1981b). Cross sectional areas and perimeters are reported for more than 29 locations along the airpath. These measurements allow for estimating the volumes, surface areas and other parameters, such as the gas phase mass transfer coefficient, necessary for dosimetry modeling. On the other extreme, only the length, volume and surface area of a species URT may be reported (e.g., Swenberg et al., 1983). Other models (e.g., Kliment, 1973; Schreider and Hutchens, 1980) have more than one segment but may give only the lengths and volumes. With surface areas for each segment, even these simplistic URT anatomical models could prove useful in dosimetry modeling.

Liquid Lining

URT and Tracheobronchial Region

The epithelium of the upper respiratory tract of mammals is covered by a two layer liquid, a continuous blanket (Morgan et

al., 1984) of viscous mucus, the epiphase, overlying a serous (periciliary) fluid, the hypophase, in which the cilia move in a coordinated fashion (Lucas and Douglas, 1934). Major functions of the mucus-serous-cilia system are discussed by Kaliner et al. (1984).

In the TB region, the liquid lining is similar to that of the URT; it also is composed of a watery-like layer, the periciliary fluid bathing the cilia to their tips (see Fig 1). This layer is covered by mucus throughout much of the TB region. In airways where mucus is normally found, this lining may or may not be continuous, a matter in dispute. In the smallest bronchioles of healthy animals there is no mucus (Gil and Weibel, 1971).

There are two basic concepts as to the extent to which mucus covers the periciliary liquid. In one view mucus forms a continuous blanket (Luchtel, 1978; Kaliner, 1984); whereas others view the mucous layer as not being continuous, but rather being made up of flakes and droplets (Fig 1. see Van As, 1977; Jeffery and Reid, 1977). In either case, various thickness values for mucus have been reported suggesting large thickness variations in airways of the same generation as well as in a given airway. Thus, there could be selective locations in airways of the same generation that are at different risk from exposure to inhaled gases. From the viewpoint of dosimetry modeling and predicting the quantities of absorbed gas by a given compartment (mucus layer, periciliary layer, the cilia and the epithelial layer,

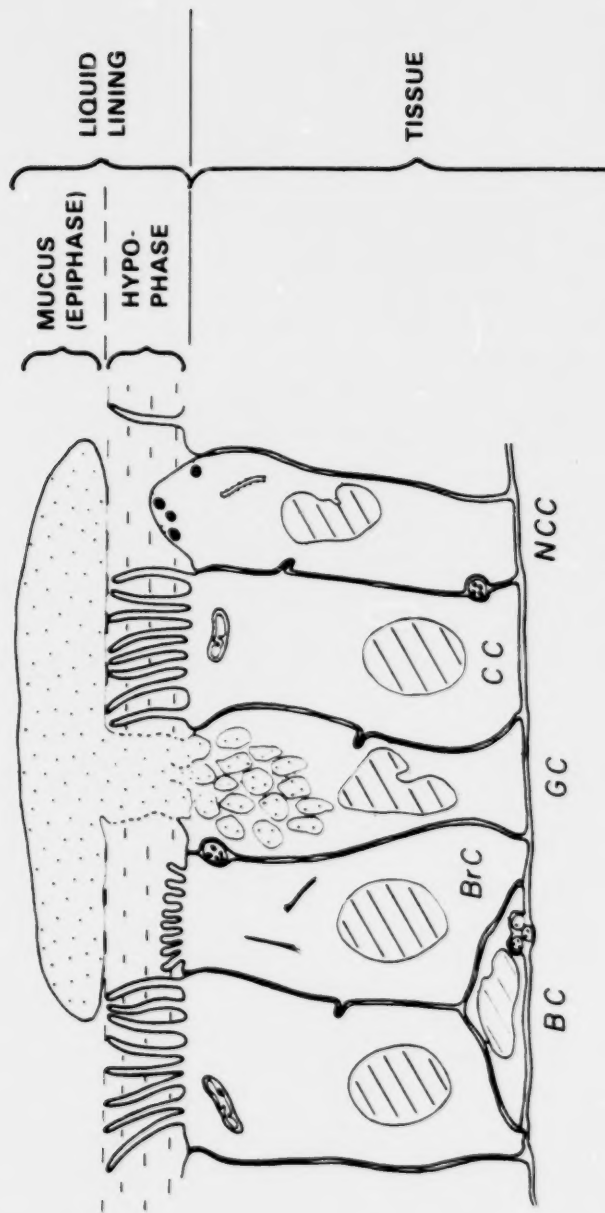


Figure 1. Diagrammatic representation of the airway epithelium. Luminal or superficial cells represented are ciliated (CC), goblet or mucous (GC), nonciliated serous (NCC) and brach (BrC). A basal cell is labeled BC. As representing one view, the epiphase or mucus layer is pictured as discontinuous, being made up of flakes. The hypophase is composed of a low viscous periciliary fluid in which cilia beat or move in such a way as to propel mucus toward the glottis. (Reproduced from Jeffery and Reid, 1977, with modification.)

etc.), the thickness distribution of mucus, as a function of location, is of considerable importance.

The periciliary layer is about as thick as the cilia are long, 4 to 6 μm , depending on location. In some cases, micrographs show cilia tips penetrating into the overlying mucus, giving the beating cilia a greater hold on the mucus to propel it towards the trachea. Whether or not the periciliary layer is thinner than 4 to 6 μm in the regions not occupied by groups of ciliated cells apparently is not discussed in the literature.

Going from the TB region to the pulmonary region, the liquid lining most probably is continuous with the thinner lining of the pulmonary region; however, we know of no quantitative description of the transition. Since this transition region is a place of maximum damage for some gases, such as NO_2 and O_3 , an understanding of lining thickness here could be important in quantifying centriacinar uptake.

Most of what is known about the chemical constituents of the TB region liquid lining comes from lavage data from patients with pulmonary diseases such as asthma, cystic fibrosis, and chronic bronchitis. Only recently has data been obtained from patients without lung problems (e.g., Woodward et al., 1982). However, techniques are still needed to collect the periciliary fluid as present approaches recover mostly the mucus of the epiphase (Boat and Cheng, 1980). Lavage fluid is separated into two components, the insoluble constituents called gel and the solubles in the sol

portion. This latter watery substance may or may not be chemically similar to the periciliary fluid. Mucus (gel) has four major constituents: glycoprotein (2% - 3%), lipids (0.3%-0.5%), proteins (0.1-0.5%), and water (95%) (Lopez-Vidriero and Reid, 1980). However, disease may modify the constituents from that of healthy persons.

Some of the major unsaturated fatty acids and their effective concentrations (for reacting with O_3) found in the constituents of lavage fluids and other lung fluids and tissue are given by Miller et al. (1985). Although the data for mucus are not complete, they are such that the effective fatty acid concentrations are based on 70-80% (by weight) of the lipids in the mucous samples.

Pulmonary Region

The pulmonary epithelium is considered to be covered, at least in part, by an acellular lining composed of a serous fluid, possibly serum transudate, from 0.01 to as much as several microns in thickness, but on the average about 3% to 5% of the air barrier thickness (Weibel, 1973). Covering this fluid and separating it from air is a 0.002 to 0.01 μm thick surface active monomolecular film called surfactant (Clements and Tierney, 1965).

Hills (1982) has suggested the possibility of a discontinuous pulmonary liquid lining, the pulmonary surfaces being largely dry. Obviously, the uncertainty in the physical nature of the pulmonary acellular lining presents similar problems to dosimetry modeling and to the interpretation of toxic effects as does the uncertainty in the nature of the TB region liquid lining.

Information on the chemical composition of the pulmonary region liquid lining comes mainly from analysis of the insoluble fraction of pulmonary lavage material, the soluble portion corresponding to the hypophase or the serous fluid is seldom analyzed. The insoluble part, corresponding to the monolayer surfactant material, is 80% to 90% lipid, 10% to 20% protein and 1% to 2% carbohydrates (Sahu and Lynn, 1977). The unsaturated fatty acid compositions of the insoluble part of pulmonary lavage fluid and their estimated effective concentrations are given in Miller et al. (1985). As far as absorption of gases is concerned the serous fluid because of its greater thickness probably has more influence on gas absorption than the thinner surfactant layer. Further characterization (chemical and physical) of the thicker serous layer is needed.

Lung Tissue and Blood

URT and TB Epithelial Layer

Most of the epithelium of the URT is ciliated, pseudostratified, and columnar, the type of luminal cells being the goblet and the ciliated and non-ciliated columnar cells; relative abundance depends on location (Jeffery and Reid, 1977; Mygrind et al., 1982). Whether or not ciliated, columnar cells are covered by 300 to 400 microvilli up to 2 μ long, helping to increase exchange processes across the epithelium as well as preventing dryness (Mygrind et al., 1982). Most columnar cells are ciliated.

Cells of the luminal epithelium of the TB region are classified as ciliated and non-ciliated. Non-ciliated cells can be further classified as secretory or non-secretory. Secretory cells are the serous, Clara and goblet cells. Brush and intermediate cells make up the non-secretory cells. The relative numbers and types of cells depend on location in the respiratory tract as well as on species (e.g., Castleman et al., 1975). Fig. 1 illustrates some of these cells and their relationship to the liquid lining.

Pulmonary Tissue and Capillary Blood

Respiratory bronchioles, if present, are transitional airways and their cellular make-up reflect this. The cells change in nature on moving distally from the terminal bronchioles. For example, in monkeys the cells are initially cuboidal in shape and are replaced toward the end of respiratory bronchioles by squamous type cells similar to alveolar Type I cells (see e.g., Castleman et al., 1975). In addition, the respiratory bronchioles have outpockets of alveoli that increase distally in number.

The tissue of alveolar septum (Fig. 2) is, for the most part, a three layered structure composed of the epithelial lining, an intermediate interstitial sheet, and the capillary endothelial lining. The latter lining is made up of simple squamous cells that are thin and cover large areas. The two major cell types of the pulmonary epithelium are the Type I and Type II. Type I cells are similar to endothelial cells with broad thin cytoplasmic

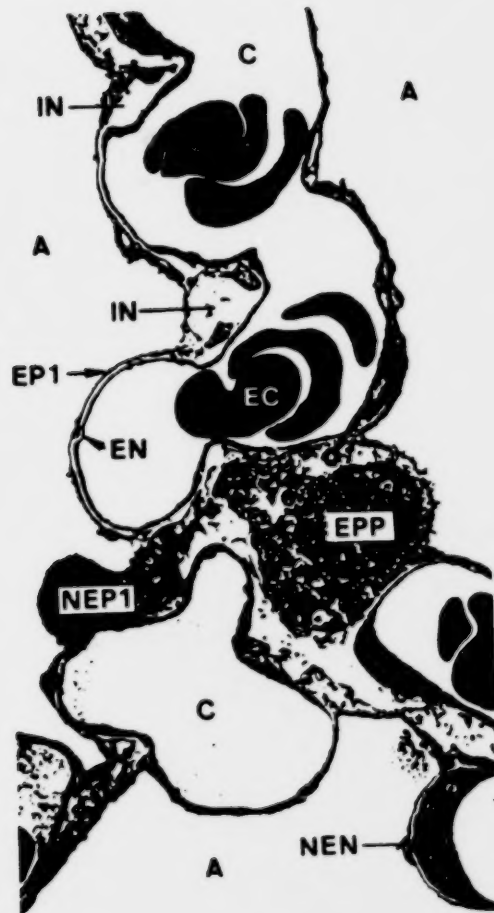


Figure 2. Electron micrograph of interalveolar septa. (Reproduced from Gehr et al., 1978; with modifications). Indicated are alveolar capillaries (C) containing erythrocytes (EC), endothelial cells and nuclei (EN and NEN, respectively), type I and II epithelial cells (EP1 and EPP, respectively), the interstitial space (IN) and the alveolar air space (A).

sheets extending from a bulkier nuclear region. This thin (0.1 to 0.2 μ thick) cell contributes to efficient gas exchange (Burri, 1985) as it covers from 90 to 97 percent of the alveolar surface area. Type II cells are cuboidal and believed to be the source of surfactant (Burri, 1985).

Capillaries are an integral part of the pulmonary alveolar structure (Fig. 2). Blood, which flows through the capillaries, is composed of plasma and blood cells in about the equal proportion. Gases not depleted by reactions in the air-blood barrier may penetrate to capillary blood where further reactions with blood components are possible.

The chemical make up of tissue and blood is not much different than that of the liquid lining, mainly water with traces of glycoproteins, lipids, and proteins, as well as smaller molecules. However, the relative amounts or concentrations of the molecular components of the major constituents can be very different (Miller et al., 1985).

PHYSICAL AND CHEMICAL FACTORS

In general, the absorption of gases will be affected by diffusion, convection, and, if relevant, chemical reactions in the gas phase (lumen and airspaces) as well as by solubility, diffusion, convection, and chemical reactions in the liquids and tissues of the respiratory tract. This section is concerned with absorption in respiratory tract tissues and fluids. Discussed are the concepts and nature of solubility, diffusion, convection and

chemical reactions as these factors are expected to apply. A discussion of gaseous transport in the lumen of the airways is found in the Chapter by Ultman.

Solubility

Solubility refers to the ability of a medium to absorb a gas. There are many different definitions for solubility, including the Bunsen, the Kuenen, the Ostwald, the absorption, and Henry's Law (Clever and Battino, 1975). In equilibrium conditions these definitions relate quantities of a gas in the gas phase to quantities of the gas in a liquid. For dosimetry modeling, one of the most convenient definitions of solubility is Henry's Law expressed as $C_g = HC_l$, where C_g and C_l are, respectively, the gas and liquid phase molar concentrations of the absorbed gas and H is Henry's Law constant for this particular formulation. This law only applies to the free or uncombined form of a trace gas in solution, and can be used to quantify the concentration of the molecular form of the trace gas in a liquid, even if the absorbed gas is involved in chemical reactions. The constant is a function of temperature and the molecular properties of the liquid and the gas; however, for constant temperature and the ranges of ambient concentrations of trace gases the coefficient, H , can be considered constant.

Henry's Law constants have been determined for many gases in water (e.g., NRC, 1977; Altman and Dittmer, 1971). Often these values are used as approximations for in vivo values. Altmer and

Dittmer (1971) give data on Henry's Law constants for a few gases (O_2 , NO_2 , CO_2 ; e.g.) in water, and several biological fluids and tissues. In general, there is not much variation in the constant for a given gas among the various substances represented. Except for a few cases, the use of the water value would seem justifiable. Although the data is incomplete, they suggest that the value of Henry's law constant is not influenced much by different biological tissues and liquids, suggesting that a known value for one tissue or liquid is a good approximation for missing values.

Henry's law can be extended to trace gases in equilibrium in two different media with a common interface. In this situation the ratio of the concentrations in the two media is the ratio of the Henry's law constant of the two gases. This ratio is called the distribution coefficient or the partition coefficient.

Altman and Dittmer (1971) give a table of partition coefficients for several biological tissues and fluids. The values are close to one (to within 15%) suggesting that animal fluids and tissues are very similar with respect to Henry's Law constant.

Molecular Diffusion

Molecular diffusion is a result of the random motions of molecules, an effect that redistributes molecules in such a way that there is a net flow from regions of high concentration to regions of lower concentration (Danckwerts, 1970). The process often is described in terms of the diffusional flux, which is the net rate

of transfer of mass or molecules across a plane perpendicular to a given direction due to the random motions. Mathematically, the flux is expressed as (Danckwerts, 1970), $F = -D \, dc/dx$, where dc/dx is the concentration gradient along the given direction; F is the diffusional flux. The formula is often referred to as Fick's law and can be used to describe diffusion in gases, liquids and tissues. D is the molecular diffusion coefficient and is defined by the above equation. Its units are $(\text{length})^2/\text{time}$ and its value depends on the properties of the molecule and the medium.

According to Sherwood et al. (1975) the diffusion of small molecules such as O_2 and CO_2 in solutions of biological proteins is approximately the same as in polymer solutions; however, the effect of polymers on diffusion, does not follow a simple pattern. Nevertheless, the diffusion coefficients of small molecules in dilute polymer solutions of similar constituents as biological fluids and tissues are probably similar to, but smaller than, the water value. Most likely for small molecules other than O_2 and CO_2 , such as O_3 , NO_2 , and formaldehyde ($HCHO$), these conclusions are applicable. Unfortunately, for the larger biological molecules, diffusion coefficients may be difficult to estimate from water values and measurements in biological substances may be necessary.

The molecular diffusion coefficient of a few gases, such as O_2 and CO_2 , in biological fluids and tissues have been measured. Values are generally less than in water. For example the values for O_2 in water, ox serum, frog muscle, dog connective tissue, and

rat lung tissue are, respectively, 3×10^{-5} , 1.7×10^{-5} , 1.2×10^{-5} , $.97 \times 10^{-5}$, and 2.3×10^{-5} cm²/sec (37°C; Altman and Dittmer, 1971).

Convection in Respiratory Tract Fluids

There are two lung fluids in which convection may play a role in the absorption of reactive gases, the liquid lining of the URT and the TB region, and capillary blood. Both fluids are in motion and absorption may be enhanced by the removal of absorbed gases from a location or the replenishing biochemical reactants.

In order to be able to account for convection (in modeling) the flow rates of the fluids are needed. In some cases, mucous flow rates in the URT (e.g., Morgan et al., 1984) and airways of the TB region have been measured (e.g., Iravani and van As, 1972). In addition, estimates of rates in all airways have been made based on clearance data from selected airways, anatomical data, and other assumptions (e.g., van As, 1977; Miller et al., 1978). For example, Velasquez and Morrow (1984) applied kinetic equations to data on particle retention in five airway zones (based on airway diameter) of guinea pigs to estimate transport rates in each airway generation. The calculated mucociliary (particle) rates ranged from 0.001 mm/min in the distal bronchioles to approximately 8 mm/min in the trachea. However, mucociliary rates are not necessarily the same as the liquid lining flow rates and further data or assumptions must be used to estimate convection velocities.

Pulmonary capillary blood flows have been measured (e.g., Horimoto et al., 1981), as well as theoretically calculated (e.g., Zhuang et al., 1983). We are not aware of capillary blood flow measurements for the URT and the TB region; no doubt reasonable estimates can be obtained if needed. Because the "air-blood" barrier in these regions is much thicker than it is in the pulmonary region, reactive gases (within the scope of this paper) will not reach the capillaries proximal to the pulmonary region. However, Heck et al. (1983) demonstrated that either HCHO or (most probably) its reaction products were transferred to extrapulmonary tissues and fluids outside the URT. Also, NO₂ products are known to be transferred out of the lung (Postlethwait and Mustafa, 1981). Presumably, capillary blood flow is a major factor in the transfer, suggesting that in developing dosimetry models the effect on gas absorption by product removal from the lung by blood must be considered.

Chemical Reactions

Chemical reactions occur as a result of the collision of molecules whereby the interaction of the colliding molecules (reactants) result in one or more different molecules (products). For modeling purposes, the rates of reaction or the rates of change of concentrations (e.g., moles per liter per second) are important because the rates are the means whereby the loss and gain of chemical species are quantified. In general, rates are a complicated function of the local concentration of each of the

reactants and products involved.

Theoretically, all of the chemical species involved and the reaction rate constants are needed to characterize a reacting system for modeling purposes. In practice, however, complete information is not always available; even if rates are known, the products or their formation rates, or both, may not have been measured. This poses no problem in modeling systems of reacting compounds if the unknown products do not react significantly with the known species. Even if this is not the case, approximations are often possible that will allow the modeling of absorption of the reacting gases.

Much of the theoretical formalism for the absorption and chemical reaction of gases in thin films found in chemical engineering and mass transfer books (e.g., Danckwerts 1970; Astarita, 1967) are applicable to the thin layers of the liquid lining, tissues, and capillaries of the lung. The formalism of film theory is most relevant since turbulence is not expected to be a transport mechanism of importance. Disturbances due to cilia and blood motion may prove the exception; however, these processes can be taken into account if necessary.

The main constituent of lung tissue and fluids is water, 85 - 95 percent; thus, the chemistry of absorbed gases in water is of interest. Many toxic gases react with water affecting the absorption rate, as well as creating products that may be important in further reactions with the absorbed gases and the biological

constituents. Ozone, NO_2 , SO_2 , NH_3 , and CO_2 , common in the atmosphere, react with water, as well as interact in water (see Durham et al., 1981, 1984) leading to sulfate, bisulfite, nitrite, and nitrate molecules, and the potential for changing pH. The water reactions could have an indirect or direct adverse effect on tissue and fluids.

With the introduction of biochemical constituents the reacting system will become more complex. However, depending on conditions, some of the reactions will be more important than others. If necessary, the important reactions can be determined by chemical kinetic modeling to gain information that will allow simplifying the system for use in dosimetry modeling by keeping only the important reactions.

Formaldehyde, NO_2 , and O_3 are toxic reactive gases derived from mobile sources. Their reactions with lung constituents are briefly discussed as examples of the types of reactions that should be considered in formulating dosimetry models.

Formaldehyde a necessary biochemical substance, involved in metabolism, and in small quantities not toxic; it is extremely reactive, even with itself and the unhydrated form reacts rapidly with water (Madestau, 1982; Gerberich, 1980; NRC, 1981). It is highly reactive with amines and reacts with proteins, amino acids, nucleic acid and histones as well (NRC, 1981). DNA has also been found to be damaged by HCHO (Ballenger, 1984), implying that DNA is directly attacked by or reacts with HCHO reaction products.

The reactive compounds are thought to bind to specific sites on single stranded DNA. HCHO does not react with double stranded DNA (Swenberg et al., 1983). A two-step mechanism has been suggested for the reaction of HCHO with amino groups, such as those that compose proteins and nucleic acid. The first step is fast and reversible; the second is irreversible forming a stable product (Swenberg et al., 1983).

Nitrogen dioxide (NO_2), as well as other oxides of nitrogen such as NO, are toxic. The reactions of NO_2 with water lead to nitrous acid (HONO) which may form nitrosamines that are carcinogenic; also, NO_2 reacts with unsaturated fatty acids to form radicals leading to the auto-oxidation of unsaturated fatty acids and to nitrous acid (Pryor, 1981). Apparently, nitrite (NO_2^-) is one of the major products of NO_2 reacting in lung tissues and fluids. According to Postlethwait and Mustafa (1981) over 70% of the NO_2 absorbed by a ventilated perfused rat lung was converted to NO_2^- . They also concluded that non-water substances (i.e. biological constituents) played the major role in the conversion.

According to Menzel (1976), ozone (O_3) is the most toxic of oxidizing air pollutants, its toxic effects being a result of its oxidative properties. Although it reacts with almost all classes of biological substances, biochemical, physiological and morphological effects of O_3 indicate that cellular membranes are the site of toxicity (Menzel, 1984), suggesting lipids as a major target.

Olefins are particularly sensitive to O_3 , the Criegee mechanism being the accepted mechanism of reaction (Menzel, 1976; Pryor, et al., 1983). In this process O_3 attacks the carbon double in the unsaturated fatty acid. Other mechanisms also play a role generating toxic free radicals; however, the non-radical reaction is considered dominant for most UFA's (Pryor, et al., 1983). Although, vitamin E is known to protect both unsaturated fatty acids and entire animals against some of the effects of O_3 by scavaging radicals, the vitamin does not interfere with the non-radical Criegee process (Pryor, et al., 1983).

Rate constants for the reaction of O_3 with some biological unsaturated fatty acids are known (e.g., in CCL_4 , Razumovskii and Zaikov, 1972); however, in vivo rate constants in biological substances are for the most part lacking. For example, the extent to which O_3 is able to penetrate membranes and react with unsaturated fatty acids in lipids is unknown (Pryor, et al., 1983).

According to Pryor et al. (1983), ozone reacts with amino acids and proteins. In water the only amino acids found to react with O_3 are (in order of decreasing reactivity): cysteine, tryptophan or methionine, tyrosine, histidine, cystine, and phenylalanine. Although the mechanisms for damage to proteins are not well known, there is evidence for a radical path, and a non-radical Criegee process is possible. The reactions of O_3 with sugars and nucleic acids have not been studied; however sugar reactions are expected to be slow.

DOSIMETRY MODELING

By dosimetry models we mean mathematical or experimental models that predict, simulate or are used to explain the quantitative uptake or absorption of gases in specific regions or at specific locations. The formulation of such a model for inhaled gases requires the use of information on the physical, biological and chemical properties of the respiratory tract, as discussed previously, as well as an understanding of the nature of gas transport in the lumen and airspaces (as discussed in the previous chapter). The processes and features modeled are very complex and essential information is often missing. By its very nature, a model is a simplified representation of a real process or object; complex processes and geometries are reduced to their essences with some aspects omitted and others retained.

Using a model to explore the effects of assumptions, combined with comparisons of simulation results or predictions to experimental data leads to more useful models and, more importantly, to a better understanding of the chemical, physical and biological processes modeled. A survey of mathematical dosimetry models and their basic features is presented. This is followed by a discussion of results of using models to predict the uptake and distribution of toxic gases in the respiratory tract. Emphasis is placed on examples that illustrate the sensitivity of predicted results to uncertainties in physical, chemical, and biological factors. Finally, the relationship between dosimetry modeling and

experimental data is considered. Dosimetry models constructed out of hardware are considered in the chapter by Ultman.

Survey of Dosimetry Models

URT and Total Respiratory Tract Models

We are not aware of any URT or total respiratory tract dosimetry model which has been developed to be used to predict the absorption of toxic reactive gases. The two URT models discussed below were developed for purposes of analyzing experimental data and estimating parameters, although they could be used for predicting dose or uptake.

Chang et al. (1983) devised a very simple dosimetry model that they used to better understand species difference in nasal toxicity due to HCHO. This model, for all its simplicity, embodies most of the principals used in the most complex dosimetry models, including the use of species defining characteristics such as ventilatory and anatomical parameters. The authors defined the "dose" available for deposition on the nasal surface as the HCHO concentration times the minute volume divided by the nasal cavity surface area. Their "dose" is most probably a good estimate of the average quantity of HCHO absorbed by the URT. Chang et al. (1983) concluded that the use of their "dose" helped to better understand species differences in nasal toxicity.

Aharonson et al. (1974) developed a model based on the assumptions of mass balance, approximate steady-state, and that the flux of gas to the air-liquid lining interface is proportional to the

trace gas phase partial pressure. They applied the model data on the uptake of acetone, ether, O_3 , and SO_2 in the URT of dogs to estimate the dependence of the effective mass transfer coefficient on flow rates. Aharonson et al. (1974) concluded that the transfer coefficients of the four gases increased with increasing air flow rate.

Recommendation. In order to better understand toxic (1) effects in the URT, dosimetry models for this region are needed. Models are needed also to augment present LRT models in order to relate LRT predictions to ambient concentrations. Simple empirical models, similar to Aharonson et al. (1974),, may be sufficient if toxic effects only in the LRT are of interest.

LRT Models

In the model of McJilton and coworkers (McJilton et al., 1972; NRC, 1977; Morgan and Frank, 1977) absorption and transport in the lumen and airspaces are based on a one-dimensional differential equation that accounts for convection, molecular diffusion and the loss of gas by wall absorption. Based on the assumption that transfer was controlled by the liquid lining, the flux of gas to the air-liquid lining interface was defined in terms of a liquid lining mass transfer coefficient. Chemical reactions were not considered in the liquid lining and the transfer coefficient was based on the physical properties of O_3 and the lining (Henry's Law constant, molecular diffusion coefficient, and lining thickness)

and the requirement that the O_3 concentration at the liquid lining - tissue interface be zero. This latter requirement was based on the assumption that O_3 reacted instantaneously with the tissue constituents and could not penetrate to any significant depth in the tissue compartment (NRC, 1977).

The model was used to simulate the uptake of O_3 (and SO_2) in humans, using the airway model of Weibel (1963). This anatomical model defines the radii, length, surface areas and volumes of the lumen and air spaces of each of its 24 generation. A sinusoidal breathing pattern was assumed (lung size did not vary during "breathing"). The liquid lining thickness depended on the generation, "10 μm in the upper generations, 3-5 μm in the alveolar ducts, and 0.3 μm in the alveoli" (NRC, 1977).

The differential equation developed to take into account the above factors was solved using finite difference methods. The local dose was computed for each generation, the dose being the mass per unit area gained by the airway surface.

One of the major deficiencies in the model developed by McJilton et al. was the lack of chemical reactions in the liquid lining. Miller (1977) developed an O_3 dosimetry model to address this limitation. A second model has also been developed by Miller and co-workers (Miller et al., 1985). It differs from the first in the way it handles chemical reactions and in taking into account reactions in lung tissue and pulmonary blood.

The basic features of the first model of Miller and co-workers are described in Miller (1977) and Miller et al. (1978). The formulation of this model and the model of McJilton et al. is very similar with respect to how lumen and airspace transport is modeled, and to the use of anatomical models, mass transfer coefficients, and distally decreasing liquid lining thickness. However, differences do exist. For example, the first model of Miller uses an axial dispersion coefficient to account for air velocity inhomogeneities in place of axial molecular diffusion as used by McJilton et al. Furthermore, no assumption was made as to whether the radial flux was limited by the liquid lining. Instead a gas phase mass transfer coefficient was calculated based on an approximate radial O_3 concentration profile and combined with the liquid phase transfer coefficient to obtain an overall mass transfer coefficient. Although such enhancements make the model developed by Miller et al. (1978) more physiologically sophisticated than the one developed by McJilton et al., the additions have had a minor effect on simulation results. Nevertheless, such enhancements are necessary to determine what processes and factors are important.

Chemical reactions in the liquid lining were taken into account by assuming that the reaction rates of O_3 with the constituents of the lining were so fast that the reactions could be characterized by an "instantaneous reaction regime" similar to that discussed by Astarita (1967). In order to apply this

description the rates of the production of biochemical reactants in each generation was required. This was done by assuming that the production rates decreased distally, using tracheal mucous flow rates, using data on the surface area of each tracheobronchial generation and by specifying the concentration of the reacting biochemical constituents and their stoichiometry of reaction with O_3 (Miller, 1977; Miller et al., 1978). Mucus transport rates, such as those estimated by Valesquez and Morrow, 1984, would have been helpful in modeling the production of biochemical reactants throughout the tracheobronchial region. The concentration of O_3 was assumed to be zero at the liquid-tissue interface for reasons similar to that given by McJilton et al. Thus, O_3 did not penetrate into a tissue compartment. Nevertheless, the "tissue" did absorb O_3 - the O_3 flux to the tissue was defined as the same as the O_3 flux to the liquid-tissue interface.

The second model of Miller and co-workers (Miller et al., 1985) differs from the first mainly in how chemical reactions are modeled and in the inclusion of tissue and pulmonary blood compartments where reactions take place. The reactions of O_3 with the biological constituents of the liquid lining, tissue and blood compartments are assumed to be second order; however, the concentrations of the biological constituents remain constant during the time of simulation (see Miller et al., 1985, for justification). Thus, the model uses pseudo-first order reactions

to account for chemical reactions. The first order rate constant is the product of the net concentration of the reacting biological compounds times an effective second order rate constant. The major reactions considered in estimating the effective first order rate constant are those of O_3 with the unsaturated fatty acids. The reactions of O_3 with the amino acids and other non-unsaturated fatty acid constituents are assumed relatively ineffective (as far as dosimetry is concerned) and are not included in the estimations of the net concentration or of the effective rate constant.

Conceptually, in this latest model, transport in the gas phase is essentially the same as in the original (Miller et al. 1978) model. However, with recent modification the model accounts for varying lung dimensions during the breathing cycle (Overton and Graham, 1985), an addition having little effect on simulation results.

Mockros et al. (1985) have developed a mathematical simulation model for purposes of investigating transport, absorption and chemical reactions of toxic gases in the lower respiratory tract. This model and its predictions of LRT uptake of O_3 in man and rabbits is similar to the instantaneous reaction regime model and predictions of Miller et al. (1978).

Dosimetry Modeling Results

The results of dosimetry modeling that are presented serve several purposes: (1) to show the results of specific dosimetry

models, (2) to demonstrate the variations or sensitivity of predictions to the uncertainties in anatomical, physiological, and physicochemical parameters, (3) to illustrate the integration by models of anatomical, physiological, and physicochemical factors, and (4) to introduce research recommendations.

Influence of Anatomical and Physiological Factors

Fig. 3 is an example of simulation results of the model of McJilton et al., (see Morgan and Frank, 1977), illustrating the effect on predicted results of the modification of an anatomical model. The purpose of the simulations was to explore the effects on O_3 uptake of a modified lung geometry, possibly due to disease. Plotted for two simulations are the simulated doses of O_3 for humans versus model segment. The distance along the airpath from the trachea distally to the end of the airway model was divided into 25 segments, not necessarily corresponding to generations. Simulated "normal" O_3 uptake is illustrated by the heavy black line; the shaded areas correspond to dose increases that resulted from using the same airway model as the first except, in order to simulate a pulmonary defect, the number of airways distal to the seventh Weibel generation (segment 15) were reduced by 20%. The effect of the "pulmonary defect" is to increase the tissue dose in segments distal to the obstruction or defect. The major increases in dose occur in the pulmonary segments, where for one respiratory bronchiole segment the increase is as much as 17%. Both simulation curves have the same general shape. Dose is relatively high in

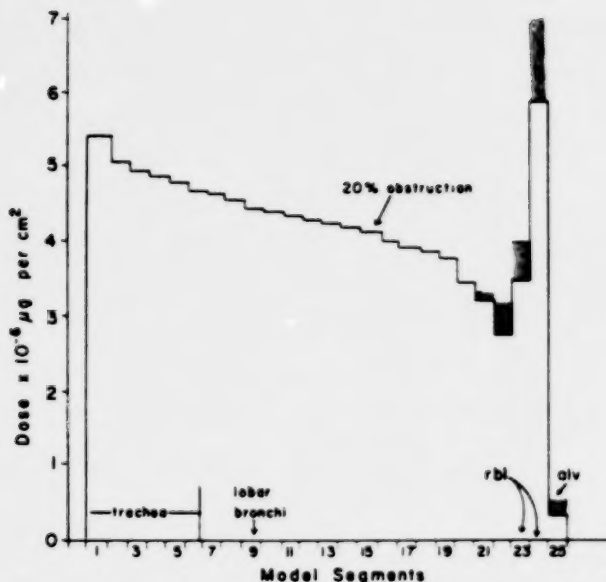


Figure 3. This figure is an example of simulation results from the model of McJilton et al. (figure from Morgan and Frank, 1977). Plotted for two simulations are the simulated doses of O₃ for humans versus model segment. The position of the trachea, lobar bronchi, respiratory bronchioles (rbl) and alveoli (alv) are indicated. Simulated "normal" O₃ uptake is illustrated by the heavy black line. The shaded areas correspond to doses increases using the same anatomical model, except that the number of airways distal to the seventh Weibel generation (model segment 15) were reduced by 20%.

the tracheas, decreasing distally to the bronchioles where, at the respiratory bronchioles, there is a sharp increase in dose followed by an even sharper decline in dose.

Overton and Miller (1985) applied the first order chemical reaction model of Miller and co-workers (Miller et al. 1985) to the anatomical models of four laboratory animals, two anatomical models each for rat and guinea pig. Simulation results for the rat are shown in Fig. 4, illustrating the effect of anatomical models on predicted dose.

The results shown in Figure 4A were obtained using the rat anatomical model of Kliment (1973) for a 160 gram rat in which airways belonging to several sequential generations are grouped into nine zones. Fig. 4B is a plot of dose(s) versus generation using the airway model of Yeh et al. (1979) for a 330 gram rat. The corresponding curves in both figures have the same basic shapes, the sharp peak in the first alveolated generation in Figure 6B being the major exception. However, according to Overton and Miller (1985), the major differences between results using the two anatomical models is in the effect of ventilatory parameters on percent uptake and on the difference in predicted percent uptake. For a constant minute volume the total uptake of the Kliment rat decreased from 93% at 80 breaths/min to only 87% at 140 breaths/min. On the other hand, at 80 breaths/min the uptake of the Yeh et al. rat was 74% (19 percentage points less than for the Kliment rat), decreasing to 50% (37 percentage points less)

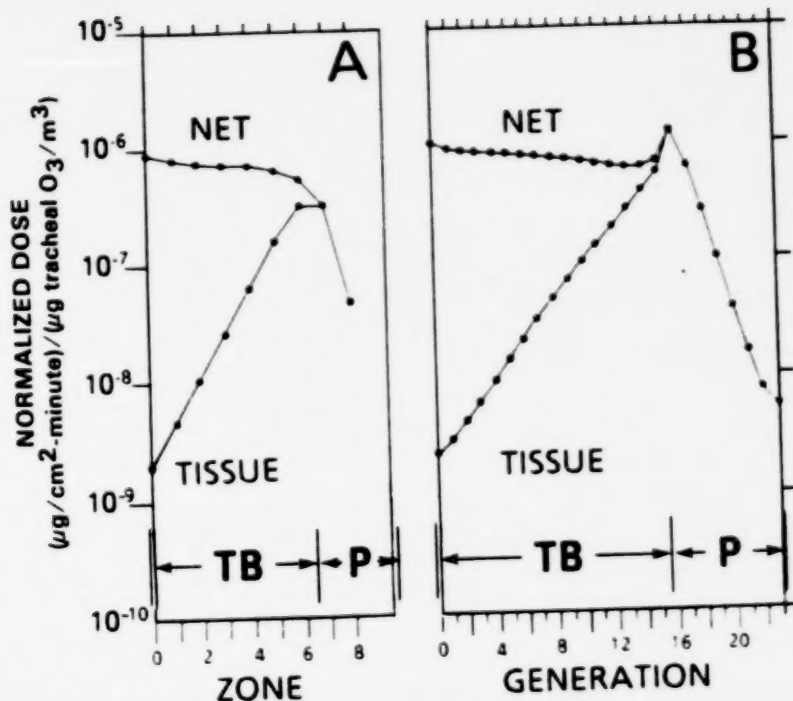


Figure 4. (Based on Overton and Miller, 1985). The use of the first order chemical reaction regime dosimetry model of Miller and co-workers to explore the effects of anatomical models on predicted O_3 dose in rat lungs is illustrated. TB = tracheo-bronchial region; P = pulmonare region. Dose normalized to tracheal concentration. A. Dose versus zone. Anatomical model from Kliment (1973); 160g rat. V_T (tidal volume) = 0.07 ml; f (breathing frequency) = 144 breaths/min. B. Dose versus generation. Anatomical model based on Yeh et al. (1979); 330g rat. V_T = 1.84 ml; f = 105 breaths/min.

at 140 breaths/min. Using allometric equations to scale the 330 gram rat to 160 gram did not reduce the Yeh et al. (1979) rat to a Kliment rat as far as percentage uptake and sensitivity to ventilatory parameters were concerned, a further indication of the importance of anatomical models in predicting uptake.

Recommendation. Develop anatomical models for different (2) subpopulations (diseased, healthy, young, old, etc.) of man and laboratory animals. These models should accurately reflect dimensions associated with physiologic conditions.

The effects of various ventilatory parameters on tissue dose is illustrated in Fig. 5. The simulations were carried out using the first order chemical reaction model of Miller et al. (1985) for the purpose of estimating the effects of exercise on tissue dose in man (Weibel, 1963 anatomical model used). The four curves presented have the same general shape, tissue dose increases distally to some generation in the pulmonary region then rapidly decreases. Where the peak tissue dose occurs depends on the ventilatory parameters, the higher the tidal volume the more distal the peak. In addition, as the ventilatory parameters increase, so does the quantity of O_3 absorbed in the pulmonary region. For the largest minute volume the pulmonary absorption is 13.6 times as much as for the lowest minute volume (resting state) for the same length of time. On the other hand, for the same increase in ventilatory parameters, the tracheobronchial absorption increased

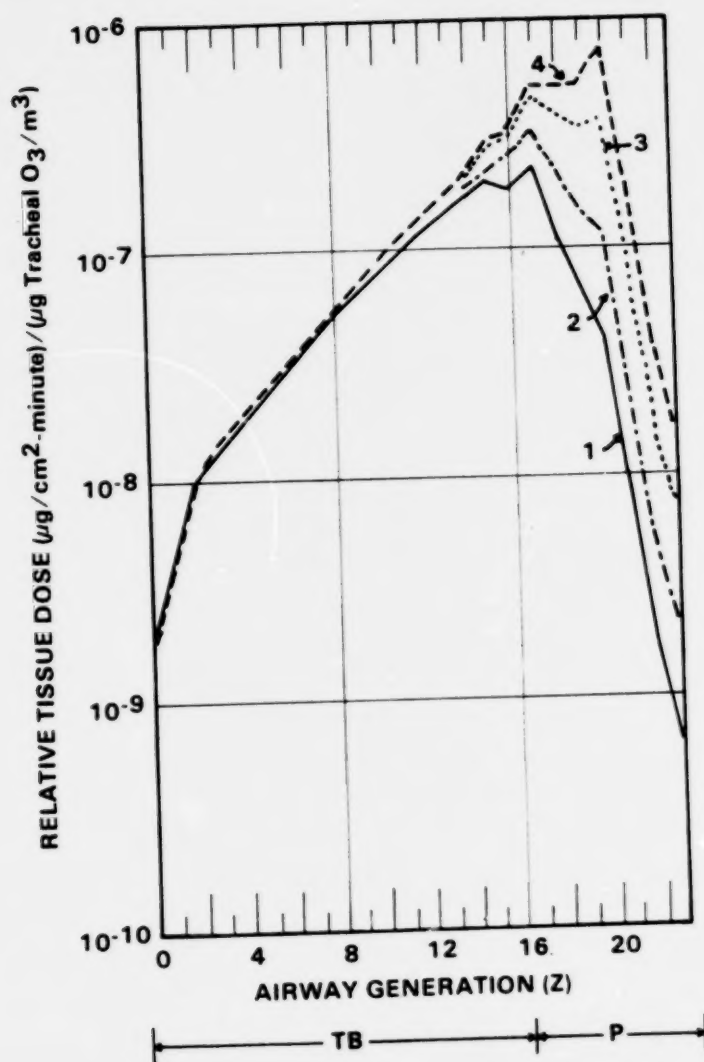


Figure 5. (From Miller et al., 1985). The use of the first order chemical reaction regime dosimetry model of Miller and co-workers to explore the effects of tidal volume (V_T) and breathing frequency (f) on predicted tissue dose of O_3 in human lungs is illustrated. Curve 1: $V_T = 500$ ml; $f = 15$ breaths/min. Curve 2: $V_T = 1000$ ml; $f = 15$ breaths/min. Curve 3: $V_T = 1750$ ml; $f = 20.3$ breaths/min. Curve 4: $V_T = 2250$ ml; $f = 30$ breaths/min. TB = tracheobronchial region; P = pulmonary region. Tissue dose has been normalized to the tracheal concentration: multiply figure values by the tracheal concentration ($\mu g/m^3$) to obtain dose ($\mu g/cm^2$ per minute).

only by a factor of 1.4. In another sensitivity study, Overton and Miller (1985) using a rat anatomical model, showed that percent uptake was sensitive to tidal volume for a given minute volume.

Recommendation. Much of the ventilatory data on (3) laboratory animals comes from anesthetized or restrained, quiet animals. Either data based on restrained or anesthetized animals should be shown to be sufficient for modeling purposes or data that corresponds to more realistic conditions should be obtained.

There are several important gaps in our understanding of the liquid lining. As of yet there is no agreement on the nature of the epiphase (mucous layer) of the liquid lining in the TB region as far as to whether or not it is continuous. More importantly, the local values of epiphase and hypophase thickness throughout the airways are needed. Likewise, the coverage nature of the pulmonary liquid lining is in dispute. A region of importance for NO_2 and O_3 is the centriacinar region where the liquid lining makes a transition from the TB region to the pulmonary; little is known about how the thickness of the liquid lining changes in going from one region to another.

Based on sensitivity studies, Miller et al. (1985) illustrate the importance of liquid lining thickness on predicted tissue dose. Their study indicates that a wide variation of tissue doses

can be predicted using the range of liquid lining thickness reported in the literature. For example, halving or doubling the liquid lining thickness in the trachea increases or decreases, respectively, the tracheal tissue dose by a factor of more than ten. The factor decreases distally to a value of about two in the first pulmonary generation. Another example in Miller et al. (1985) illustrates the effect of liquid lining thickness in the first generation of respiratory bronchioles of man; a decrease in thickness by a factor of 10 resulted in a three-fold increase in respiratory bronchiole tissue dose.

Recommendation. Obtain an accurate description of (4) the thickness of the liquid lining of man and experimental animals. This includes determining the thickness distribution of the mucous layer (epiphase) and of the hypophase as a function of airway and morphological location, and determining how the liquid lining varies in thickness in going from the terminal bronchioles into and through the first alveolated duct.

The Influence of Physicochemical Factors

The dosimetry models of Miller et al. (1978, 1985) were developed to simulate the uptake of O_3 . However, the models will simulate the uptake of any gas whose properties conform to the theoretical assumptions of the models. Based on the assumption that the properties of NO_2 met the criterion, the original model

(with the instantaneous reaction regime) was used to investigate the effects of Henry's law constant and of the mucous production rate on NO_2 uptake (Miller et al., 1982) in man (Weibel, 1963 anatomical model). At the time of the simulations the value of Henry's law constant was uncertain and the necessary quantitative data on the reactions of NO_2 with biological constituents were missing (and still are); thus the interest in a sensitivity study of the two parameters, the results of which are illustrated in Figs. 6 and 7.

Figs. 6A and 6B are dose profiles for the net quantity of O_3 absorbed in each generation and the tissue dose, respectively, for three different mucous production rates. The numbers in front of the letter K_0 (0, 0.5, 1) indicate that the mucous production rate in each generation has been multiplied by that number.

As the mucous production rate increases the amount of NO_2 absorbed in each generation increases in the tracheobronchial region, but remains the same in the pulmonary region (Fig. 6A). However, the NO_2 tissue dose (Fig. 6B) decreases in the tracheobronchial region as the production rate increases, but no change occurs in the pulmonary region where the net and tissue doses are essentially the same.

The discontinuity of the tissue dose profiles for the two largest mucous production rates is a result of the instantaneous reaction regime - either NO_2 penetrates to the tissue or it

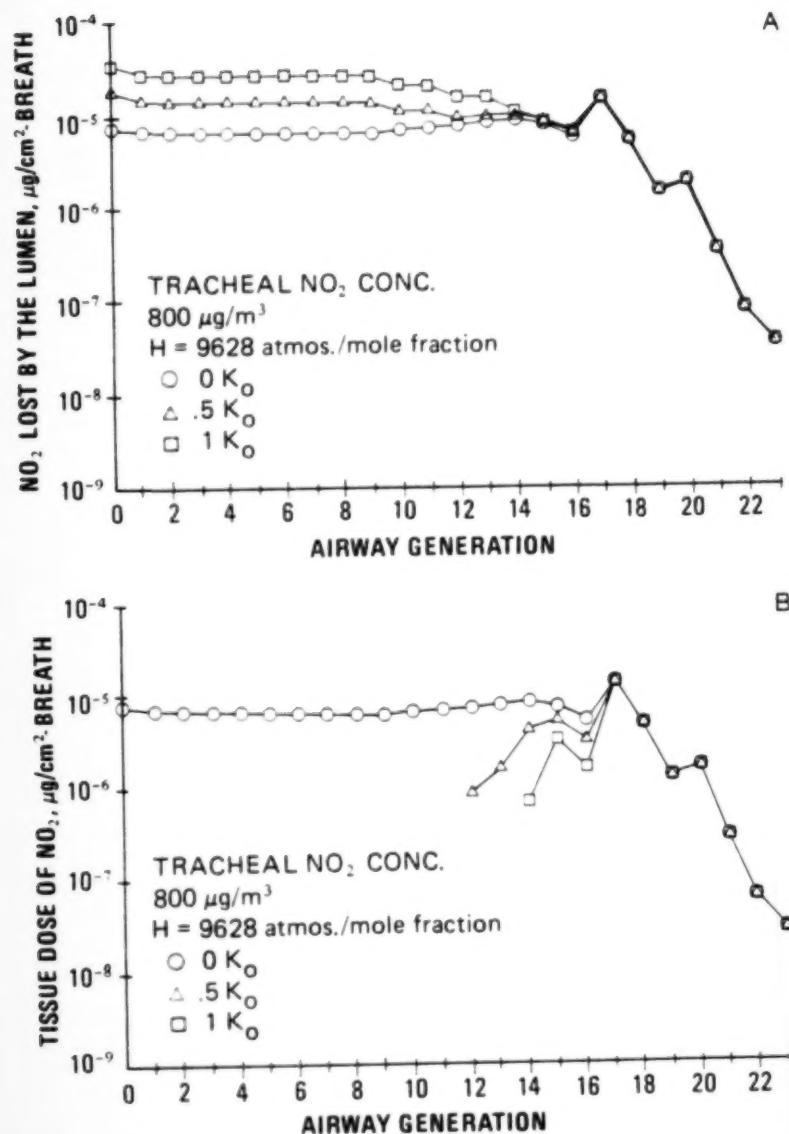


Figure 6. (From Miller et al., 1982). An illustration of the use of the instantaneous reaction regime dosimetry model of Miller and co-workers to simulate the effect of three mucous production rates on the predicted absorption of NO₂ in human lungs. H = Henry's law constant; 0 K₀, .5 K₀, and 1 K₀ indicate the simulations with no, one-half of, and the standard production rate, respectively. The tidal volume and respiration frequency are 500 ml and 15 breaths/min, respectively. A: Predicted NO₂ "lost by the lumen" or the net quantity NO₂ absorbed per unit area per breath for each generation versus generation number. B: Predicted tissue dose of NO₂ (quantity of NO₂ absorbed per unit area of tissue per breath) versus generation number.

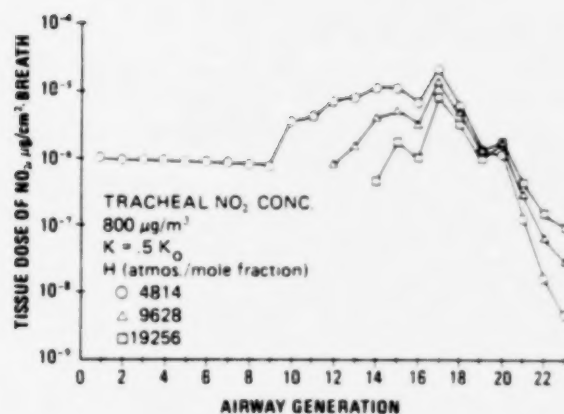


Figure 7. (From Miller et al., 1982). The use of the instantaneous reaction regime dosimetry model of Miller and co-workers to simulate the effect of three values of Henry's law constant on the predicted tissue dose of NO₂ in human lungs is illustrated. Plotted is tissue dose versus airway generation. "K = .5 K₀" indicates that one-half of the standard mucous production rate was used. Below "H" are the values of Henry's law constant used. The tidal volume and respiration frequency are 500 ml and 15 breaths/min, respectively.

doesn't. In the more recent model, in which first order chemical reactions are assumed, a similar sensitivity analysis was carried out for O_3 (Miller et al., 1985). No discontinuities occurred; however, depending on the mucous chemical rate constant, tissue dose in the trachea could be significantly less than the net dose. Otherwise, increasing the rate constant had the same qualitative effect on the net and tissue dose curves as increasing the mucous production rate did in the older model.

Figs. 6 and 7 illustrate predicted results of a dosimetry model in which the instantaneous reaction regime was used to approximate chemical reactions. The first order chemical reaction model of Miller et al., (1985) resulted in the predicted tissue doses in Figs. 4 and 5. Although there are similarities in the tissue dose profiles, there are also differences. In addition, different approximations to chemical reaction or constituent concentration can lead to different predicted uptakes. For example, for O_3 , using the Weibel geometry, and similar ventilatory parameters, the instantaneous reaction regime results in 60% uptake (Miller et al., 1978; Mockros et al., 1985); whereas, the first order reaction model gives 89% uptake (Miller et al., 1985). These differences in predicted uptake illustrate the importance of the knowledge of the kinetic mechanisms, rate constants, reactant concentrations and possibly biochemical reactant production rates.

Unfortunately, quantitative chemical information is for the most part lacking; most information available is from studies of chemical species, such as amino acids and olefins, that can be components of the major biochemical constituents. If we know the reaction chemistry of a molecule then we need to know if it reacts in the same way when it is part of a larger molecule. Such information will make data obtained in non-biological situations more useful to dosimetry modeling.

Recommendation. Determine the in vivo kinetic (5)
mechanisms of the important reactions of toxic gases with biological substances of the respiratory tract; also determine what kinetic reactions in non-in vivo conditions are applicable to biological systems; this would make the present data base more useful.

Recommendation. Identify and obtain the local con- (6)
centrations of bioreactants in the respiratory tract of different human and animal subpopulations (i.e. age, sex, health conditions, exposed to toxic gases, etc.).

The discussion on the values of Henry's Law constant and diffusion coefficients in biological tissues and fluids indicates that known values for water or for biological substances may be good estimates for missing data. Unfortunately, water or other values are not always available or they are highly uncertain. The following sensitivity study, using the instantaneous reaction

regime model of Miller and co-workers, shows that a factor of two in the uncertainty of Henry's Law constant may result in more than a factor of two difference in predicted tissue dose.

Fig. 7, from Miller et al., (1982), are plots of tissue doses of NO_2 versus generation for three values of Henry's Law constant. On the figure the value of 9628 (in units of atmospheres per mole fraction) for Henry's Law constant corresponds to a literature value. The other two values are one half and twice this value. Increasing the constant has a similar effect on tracheobronchial tissue dose as does increasing the mucous production rate (Fig. 7), the higher Henry's law constant the lower the tissue dose. A different effect occurs in the pulmonary region (generations 17 - 23). The three curves are not only separated, but cross over at the 19th or 20th generation where the lowest value of Henry's law constant results in the lowest tissue dose. However, the general shape of the tissue dose profiles from the 15th generation distally is independent of the values of the Henry's law constants used; that is, the curves increase from the 15th generation to peak at the 17th then decrease.

Recommendation. Using dosimetry models determine (7) the importance to predictions of the values of the Henry's Law constant and liquid and tissue phase molecular diffusion coefficients. Then, if necessary, measure the in vivo value of the parameters.

Dosimetry Modeling and Experimental Data

The importance of experimental uptake experiments to dosimetry modeling cannot be overemphasized. With the appropriate type of data, dosimetry modelers can obtain an idea as to the reliability of their models, infer which processes have been modeled correctly, and which ones need improvements. As previously discussed, the in vivo values of physical, biological and chemical parameters often are not well known. Using data from appropriately designed experiments, the values of some of these parameters may be estimated or refined, resulting in more reliable predictions. Furthermore, if a parameter's value is considered the same for more than one species, then values determined for one species may be applied to other species, extending the usefulness of the data.

Methods of model validation and parameter estimation are needed to provide a link or connection between experimental data and dosimetry models, as well as to provide guidelines for experimental designs. The techniques needed to compare experimental and predicted data will determine, to a large extent, the type of data needed. Unfortunately, most dosimetry experiments have not been designed for the purpose of validation and estimation (as far as respiratory tract dosimetry models are concerned). Thus, the extent to which the present data base can be used profitably with dosimetry models is limited.

Recommendation. Identify or develop methods of (8)
model validation and parameter estimation applicable to
dosimetry models of toxic reactive gases. Obtain
experimental dosimetry data for model validation and
parameter estimation. Evaluation methods and experimen-
tal designs should develop hand in hand through the
natural scientific feedback process, leading to optimal
experimental and evaluation methods. Integral to and
very much a part of this process will be the necessary
continuation of the development and refinement of dosi-
metry models.

SUMMARY

This chapter focuses on the physical, chemical and biological processes and factors involved in the absorption of reactive gases. Emphasis is placed on the importance of these factors in developing dosimetry models, special consideration being given to the role of lung fluids and tissues. Several dosimetry models are discussed and illustrations of predicted results presented to demonstrate the application of the models to the uptake of NO_2 and O_3 , and to demonstrate the use of models in determining the effects of physical, chemical and biological parameters on dosimetry predictions. Gaps in our knowledge and understanding of the processes of dosimetry are pointed out and research recommendations made to increase our understanding of the processes and to enhance the development of dosimetry models.

SUMMARY OF RESEARCH RECOMMENDATIONS

High Priority

8) Identify or develop methods of model validation and parameter estimation and obtain experimental dosimetry data for model validation and estimation.

Medium Priority

- 1) Develop complete respiratory tract dosimetry models.
- 2) Develop anatomical models for different subpopulations of man and laboratory animals.
- 4) Obtain an accurate description of the thickness of the liquid lining of man and laboratory animals.
- 5) Determine the in vivo kinetic mechanisms of the important reactions of toxic gases with biological substances of the respiratory tract.
- 6) Identify and obtain the local concentration of bioreactants in the respiratory tract.

Low Priority

- 3) Obtain ventilatory data that corresponds to realistic conditions.
- 7) Obtain values of Henry's Law constants and of liquid and tissue phase diffusion coefficients that are applicable to respiratory tract tissues and fluids.

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